Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6355–6358

TETRAHEDRON LETTERS

Studies towards diarylheptanoid synthesis. Part 2: Synthesis and ring cleavage reactions of tetrahydro-4*H*-furo[2,3-*b*]pyran-2-ones☆

Sidika Polat Cakir, Keith T. Mead* and Laura T. Smith

Department of Chemistry, Mississippi State University, Mississippi State, MS 39762, USA

Received 16 May 2003; revised 2 June 2003; accepted 3 June 2003

Abstract—Lewis acid promoted anomeric substitution reactions of a series of tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one derivatives were studied as a model for diarylheptanoid synthesis.

The blepharocalyxins represent a class of biologically active diarylheptanoid constituents recently isolated from *Alpinia blepharocalyx*.[1,2] Among them, blepharocalyxin E (Fig. 1) has shown particular promise as a potential drug candidate for the treatment of human tumors, displaying potent in vitro inhibitory activity towards human fibrosarcoma HT-1080 carcinoma cells.

The lack of general utility of fused-ring bicyclic lactones in synthesis initiated us to investigate novel applications of these structures. With the aim of laying the groundwork for a synthesis of blepharocalyxin D, we have previously shown that hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran-2-ones can act as pyranosyl donors in the stereoselective construction of thermodynamic *C*-aryl pyranosides.[3] Our goal in this study was to develop a related strategy for *C*-aryl pyranoside synthesis that could be applied to the construction of the Blepharocalyxin E framework. Toward this goal we set out to develop a stereoselective route to compounds of general structure **2**, which were viewed as potential intermediates to the final target **1** (Fig. 1). For this purpose, the use of tetrahydro-4*H*-furo[2,3-*b*]pyran-2-ones was considered as a viable option (Scheme 1). Compound **5b** appeared to be a suitable model target on which to test this strategy. Based on sound literature precedent,[3] this was expected to be formed stereoselectively by the addition of anisole to oxocarbenium ion **4** (R = CH_3), generated from the thermodynamically favored *exo*-substituted bicylic lactone derivative **3c** on exposure to Lewis acid. Herein we report the results of our preliminary investigations into this method.

For the synthesis of bicyclic lactones **3**, established protocols were adopted (Scheme 2).[4] Thus, treatment of

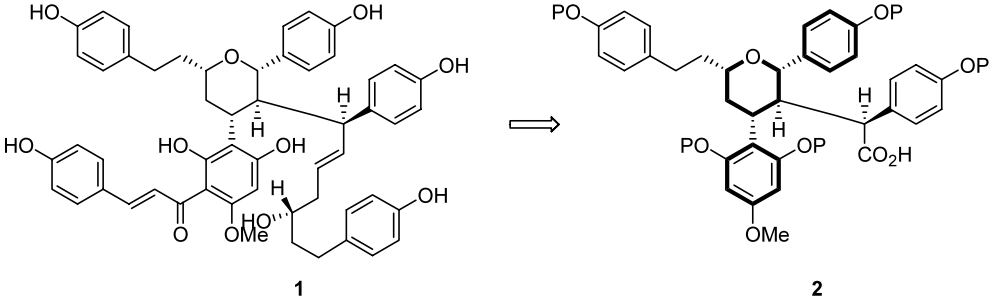


Figure 1. Partial retrosynthetic analysis of blepharocalyxin E (P = protective group).

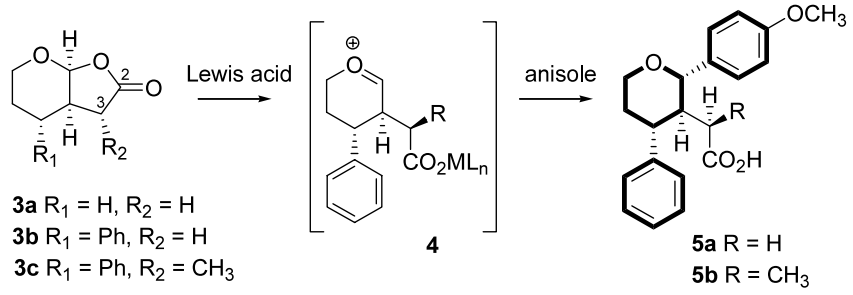
Keywords: blepharocalyxin; diarylheptanoid; oxocarbenium ion; *C*-aryl pyranoside.
☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01421-7
* Corresponding author. Tel.: (662) 325-3584; fax: (662) 325-1618; e-mail: kmead@ra.msstate.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01421-7

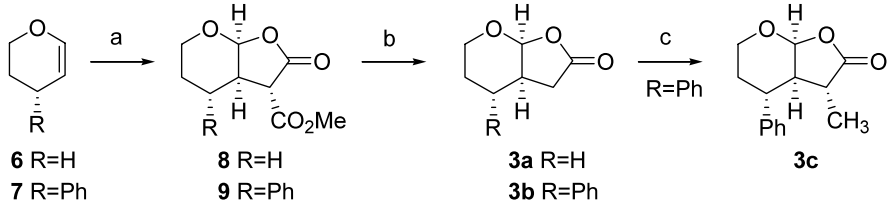
a mixture of 2,3-dihydropyran **6** and potassium methyl malonate with ceric ammonium nitrate[5] gave compound **8**, which was decarboxylated by refluxing in wet DMF to yield structure **3a**. Application of this two-step reaction sequence to racemic 4-phenyl-2,3-dihydropyran **7** provided derivative **3b** as a single isomer. The *exo* stereochemistry of compound **9**, also formed as a single isomer, was verified by X-ray crystallography. Methylation of compound **3b** with LHMDS gave the anticipated *exo* diastereomer **3c** as a single isomer.[6] Interestingly, when KHMDS was used as base, a 1:1 mixture of compound **3c** and its methyl diastereomer was formed in low yield (52%).

Ring cleavage substitution reactions of these bicyclic lactones proceeded in yields which varied from moderate to very good (Table 1), with titanium tetrachloride being the Lewis acid of choice. Remarkably, no reaction was observed with $BF_3{\cdot}OEt_2$ or TMSOTf. Predictably, hydride reductions of **3a** and **3b** yielded acid derivatives **10** and **11**, respectively (entries 1 and 2). More surprising was the observation that products formed as a single isomer in almost every case with carbon nucleophiles. The only exceptions to this were observed in the reaction of lactones **3a** and **3b** with allyltrimethylsilane (entries 3 and 4), which gave 1:1 (inseparable) and 4:1 (separable) diastereomeric mixtures of products, respectively. The major allylation product of compound **3b** was identified as compound **12** by X-ray crystallography. For other pyranoside products (entries 5–7), the stereochemistry could be readily determined from the coupling constant $J_{2,3}$. For compound **13**, for example (entry 5), this coupling constant was determined to be 4.6 Hz, clearly identifying a *cis*-stereochemistry between the C2 and C3 substituents. For compound **14** (entry 6) the value of this coupling constant was 5.8 Hz. Stereocontrol in the reactions of allyl (entry 4), alkynyl (entry 5) and *cyano* (entry 6) nucleophiles presumably arises from a kinetic preference for axial nucleophilic addition to the oxocarbenium ion intermediate[7] (see Scheme 1).

When anisole was the nucleophile, the β-stereoisomer (entry 7) was strongly favored, in agreement with related *C*-aryl pyranoside syntheses.[8] Reaction of lactone **3b** with anisole gave a single diastereomer identified as compound **5a** by the characteristic *trans* coupling constant ($J_{2,3}=9.95$ Hz). Unexpectedly, α-methylated derivative **3c** gave a completely different product under the same reaction conditions (entry 8). A single compound was isolated which was identified as the γ-lactone **15** based on it's IR and proton NMR spectral data. It is unlikely that the γ-lactone product **15** derives directly from compound **3c**, as the acyloxy group is by far the better leaving group. A more reasonable explanation is that the initial titanium carboxylate product of arylation equilibrates to structure **16** under the reaction conditions (Scheme 3). Why this did not happen with lactone **3b** is unclear, and will be a topic of future investigations. For our purposes, this unforeseen reaction did not pose a problem to our ultimate goal, as γ-lactone **15**, isolated following protolytic work-up of carboxylate salt **16**, was cleanly converted to *C*-aryl pyranoside **17**, the methyl ester of our model target **5b** (see Scheme 1), on exposure to 5% anhydrous HCl in methanol.

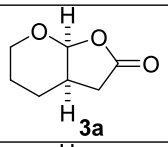
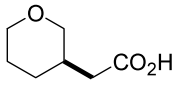
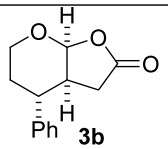
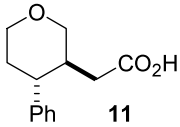
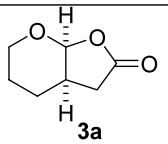
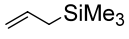
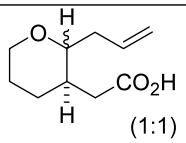
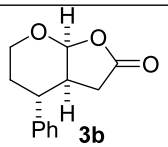
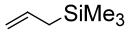
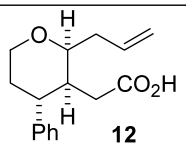
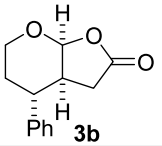
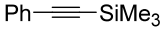
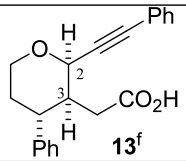
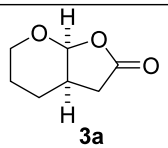
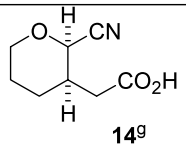
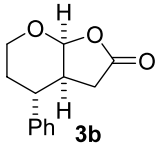
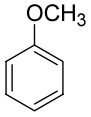
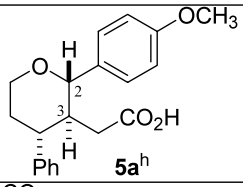
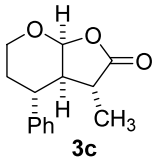
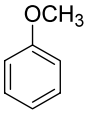
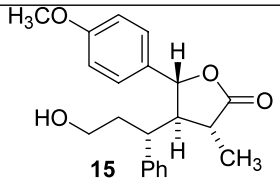


Scheme 1. Model for synthesis of compounds **2**.

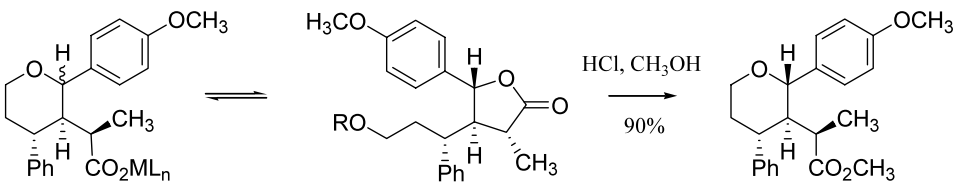


Scheme 2. Synthesis of tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one substrates. *Reagents and conditions*: (a) $CH_3O_2CCH_2CO_2K$, $Ce(NH_4)_2(NO_3)_6$, $Cu(OAc)_2$ CH_3CO_2H (40%, R = H; 52%, R = Ph); (b) DMF, H_2O, reflux (64%, R = H; 95%, R = Ph); (c) LHMDS, CH_3I, THF, −78°C (93%).

Table 1. Ring-opening substitution reactions of bicyclic lactones **3**

entry	substrate	nucleophile[a]	conditions[b]	product	%yield[c]
1	 **3a**	Et_3SiH	$TiCl_4$, CH_2Cl_2 -78°C, 1h	 **10**	67
2	 **3b**	Et_3SiH	$TiCl_4$, CH_2Cl_2 -78°C, 1h	 **11**	84
3[d]	 **3a**		$TiCl_4$, CH_2Cl_2 -78°C, 2h	 (1:1)	68
4[d]	 **3b**		$TiCl_4$, CH_2Cl_2 -78°C, 3h -40°C, 1h -20°C, 2h	 **12**	92[e]
5	 **3b**		$TiCl_4$, CH_2Cl_2 -78°C, 1.5h	 **13**[f]	56
6	 **3a**	TMSCN	$TiCl_4$, CH_2Cl_2 -78°C, 1h -40°C, 2h	 **14**[g]	71
7	 **3b**		$TiCl_4$, CH_2Cl_2 -78°C, 1.5h -40°C, 2.5h	 **5a**[h]	74
8[i]	 **3c**		$TiCl_4$, CH_2Cl_2 -40°C, 2.5h	 **15**	85

[a]Unless otherwise stated, 2 equivalents of the nucleophile were used; [b]Reactions were carried out at a concentration of 0.05M. Unless otherwise stated, 2 equivalents of $TiCl_4$ were used; [c]Yields refer to isolated products; [d]4 equivalents of the nucleophile were used; [e]Formed as a 4:1 mixture of diastereomers. The stereochemistry of the major isomer (shown) was determined by x-ray crystallography; [f]$J_{2,3}$=4.6 Hz; [g]$J_{2,3}$=5.8 Hz; [h]$J_{2,3}$=9.95 Hz; [i]4 equivalents of both nucleophile and $TiCl_4$ were used.



16 R = ML_n
15 R = H

17

Scheme 3.

In summary, Lewis acid promoted ring cleavage substitution reactions of tetrahydro-4*H*-furo[2,3-*b*]pyran-2-ones have been demonstrated for the first time and appear to be particularly useful for the synthesis of β-*C*-aryl pyranosides. Moreover, the stereochemical bias imposed by the tetrahydrofuropyranone ring system is conducive to the synthesis of structures related to blepharocalyxin E (see Fig. 1). To that end, we are currently pursuing routes to C3-arylated bicyclic lactones.

X-Ray crystallographic data: Crystallographic data (excluding structure factors) for structures **9** and **12** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC 192335 and 208762, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

References

1. Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett*. **2000**, *41*, 5903–5907.
2. Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull*. **2001**, *24*, 525–528.
3. See the preceding article in this journal, *Tetrahedron Letters* **2003**, *44*, 6351.
4. del Rosario-Chow; Ungwitayatorn, J.; Currie, B. L. *Tetrahedron Lett*. **1991**, *32*, 1011–1014.
5. D'Annibale, A.; Trogolo, C. *Tetrahedron Lett*. **1994**, *35*, 2083–2086.
6. For examples of stereoselective alkylations of related fused-ring structures, see: Depres, J.-P.; Greene, A. E. *J. Org. Chem*. **1980**, *45*, 2036–2037.
7. For an explanation for this stereoelectronic preference, see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp. 209–221. For examples of this type of preferential axial attack, see: (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976–4978; (c) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc*. **1985**, *107*, 4289; (d) Schmidt, R. R.; Hoffmann, M. *Tetrahedron Lett*. **1982**, *23*, 409; (e) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett*. **1984**, *25*, 2383; (f) Brown, D. S.; Bruno, M.; Davenport, R.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.
8. For examples, see the preceding article, *Tetrahedron Letters* **2003**, *44*, 6351, and: (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett*. **1984**, *25*, 2383; (b) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett*. **1989**, *30*, 833–836; (c) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumara, S. *J. Org. Chem*. **1998**, *63*, 2307–2313; (d) Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc*. **2001**, *123*, 6937–6938.